CONVEGNO NAZIONALE

Let's stop HIV

Nuove prospettive
e popolazioni speciali

Il ruolo dell'immunità cellulo-mediata

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Vaccino HIV: il ruolo della immunità cellulomediata

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Why Do We Need A Vaccine For HIV?

FDA-Approved Antiretroviral Drugs

NRTI
- Zidovudine
- Didanosine
- Zalcitabine
- Stavudine
- Lamivudine
- Abacavir
- Tenofovir
- Emtricitabine

NNRTI
- Nevirapine
- Delavirdine
- Efavirenz
- Etravirine

PI
- Saquinavir
- Ritonavir
- Indinavir
- Nelfinavir
- Amprenavir
- Lopinavir
- Atazanavir
- Fosamprenavir
- Tipranavir
- Darunavir

Fusion Inhibitor
- Enfuvirtide (T-20)

Entry Inhibitor
- Maraviroc

Integrase Inhibitor
- Raltegravir

Combinations
- 6 available, combining 2 or 3 drugs

Why Do We Need A Vaccine For HIV?

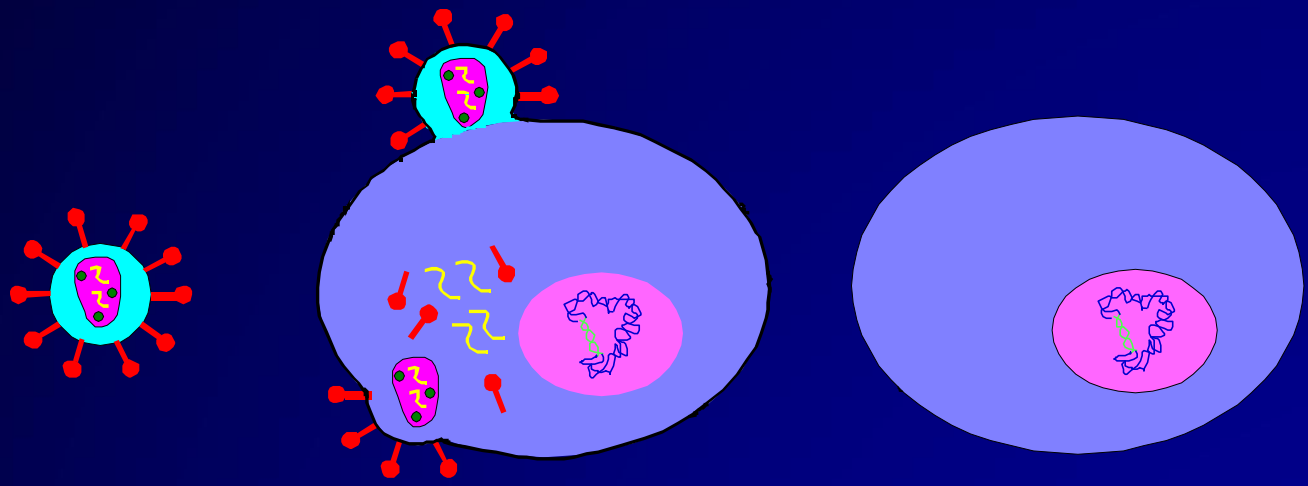
In the light of results from PrEP and PEP trials, and reduced drug toxicity, why should we invest in vaccine development?

- **The drugs are still not free of toxicity**
- **An effective vaccine is most cost-effective solution**
- **Identification of those infected or at risk is often challenging**
- **Easiness of use**
  - **PrEP and PEP are only as good as the ability to deploy them**
  - **Vaccine is given once and lasts a lifetime**

Still more than 5000 infections a day globally

WHAT SHOULD AN HIV VACCINE DO?

The Role of Vaccine-Inducible Immune Responses in Different Phases of HIV Infection



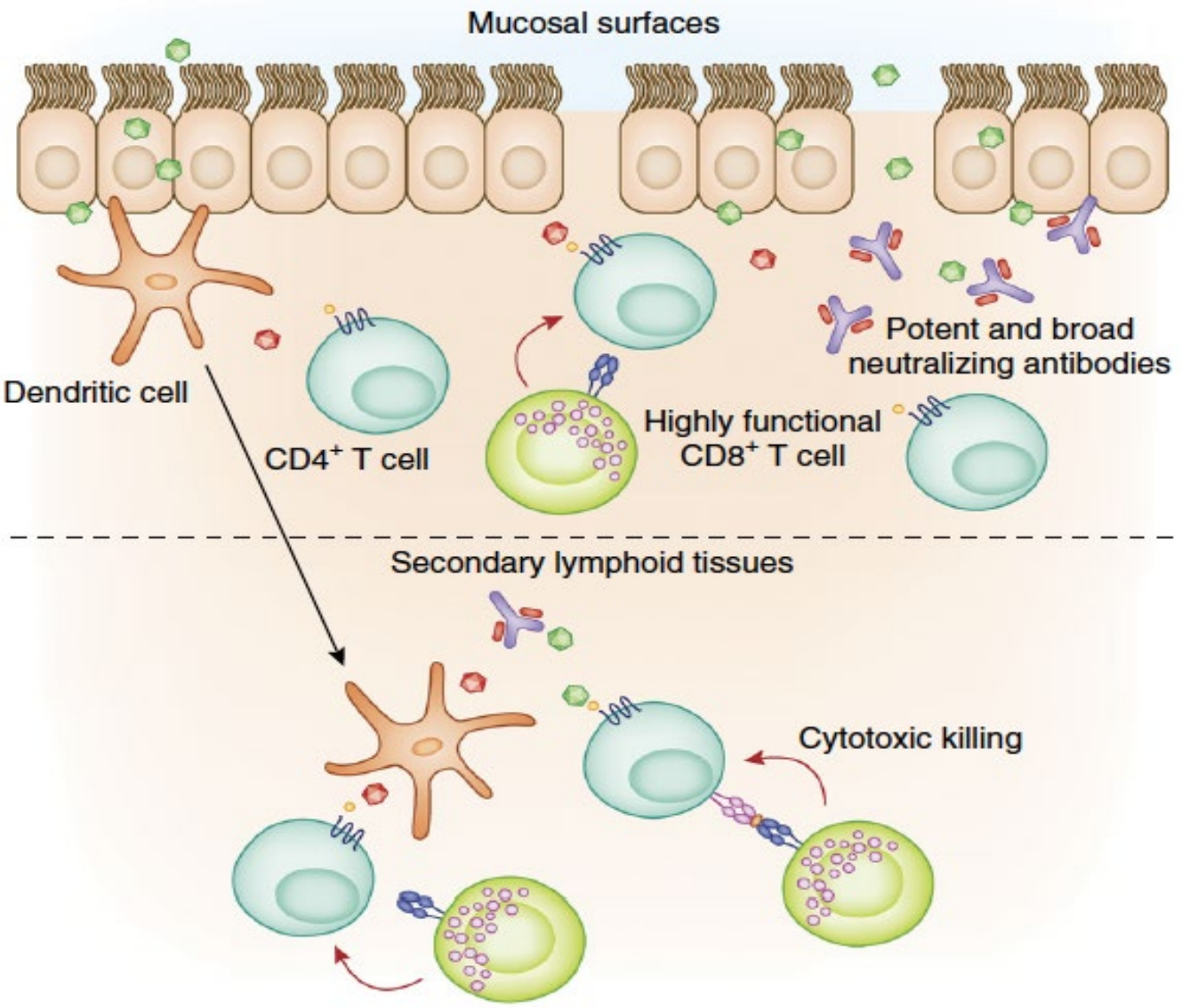
Antibody	+++	+/-	-
T cells	-	+++	-

WHAT SHOULD AN HIV VACCINE DO?

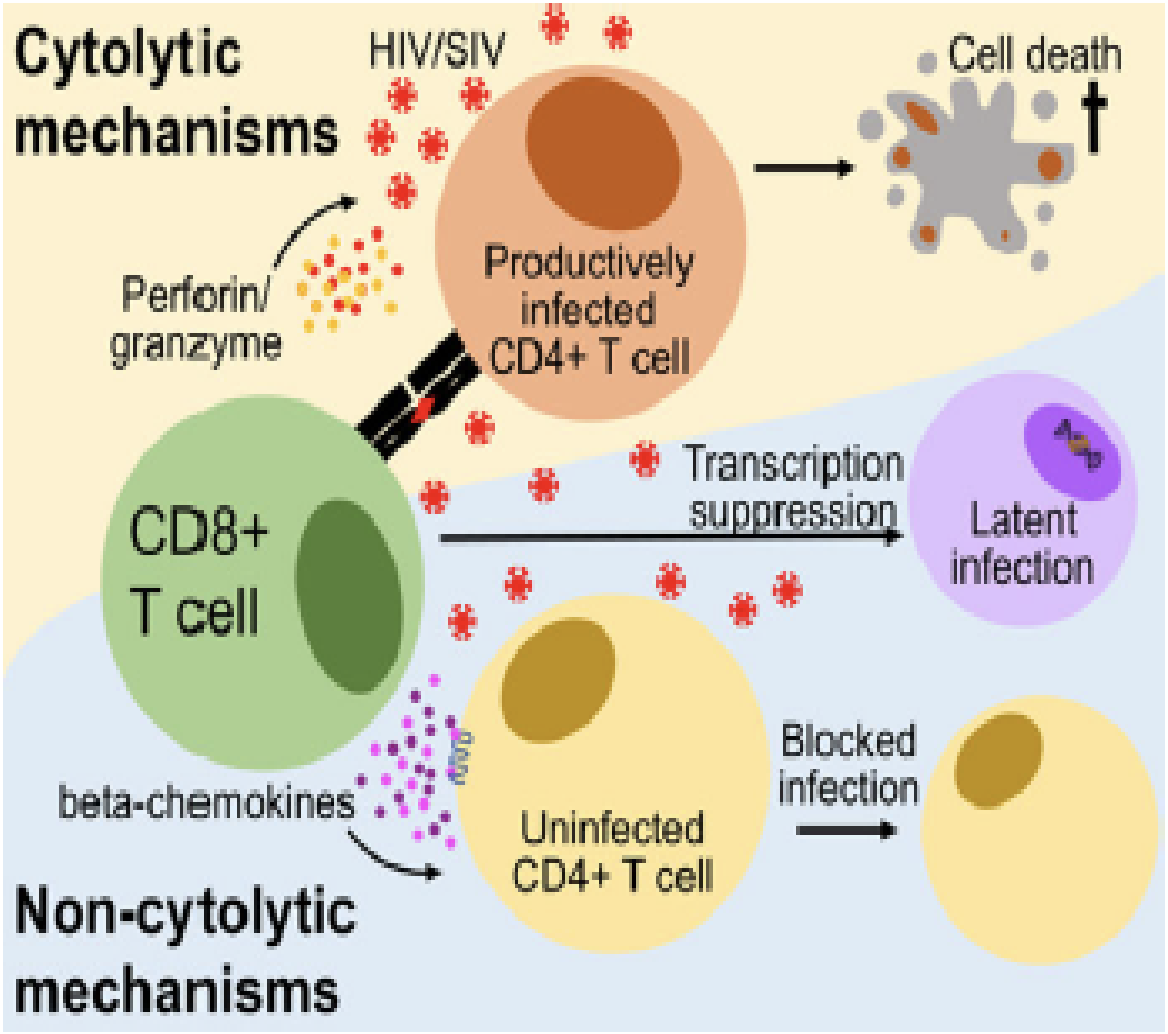
More than 90% of HIV infections are sexually transmitted: an efficient preventive vaccine MUST elicit mucosal antibodies (IgA) as well as mucosal and systemic CTL

Vaccines that aim at eliciting systemic immune responses alone are not likely to be enough: once HIV is in the blood the game is lost

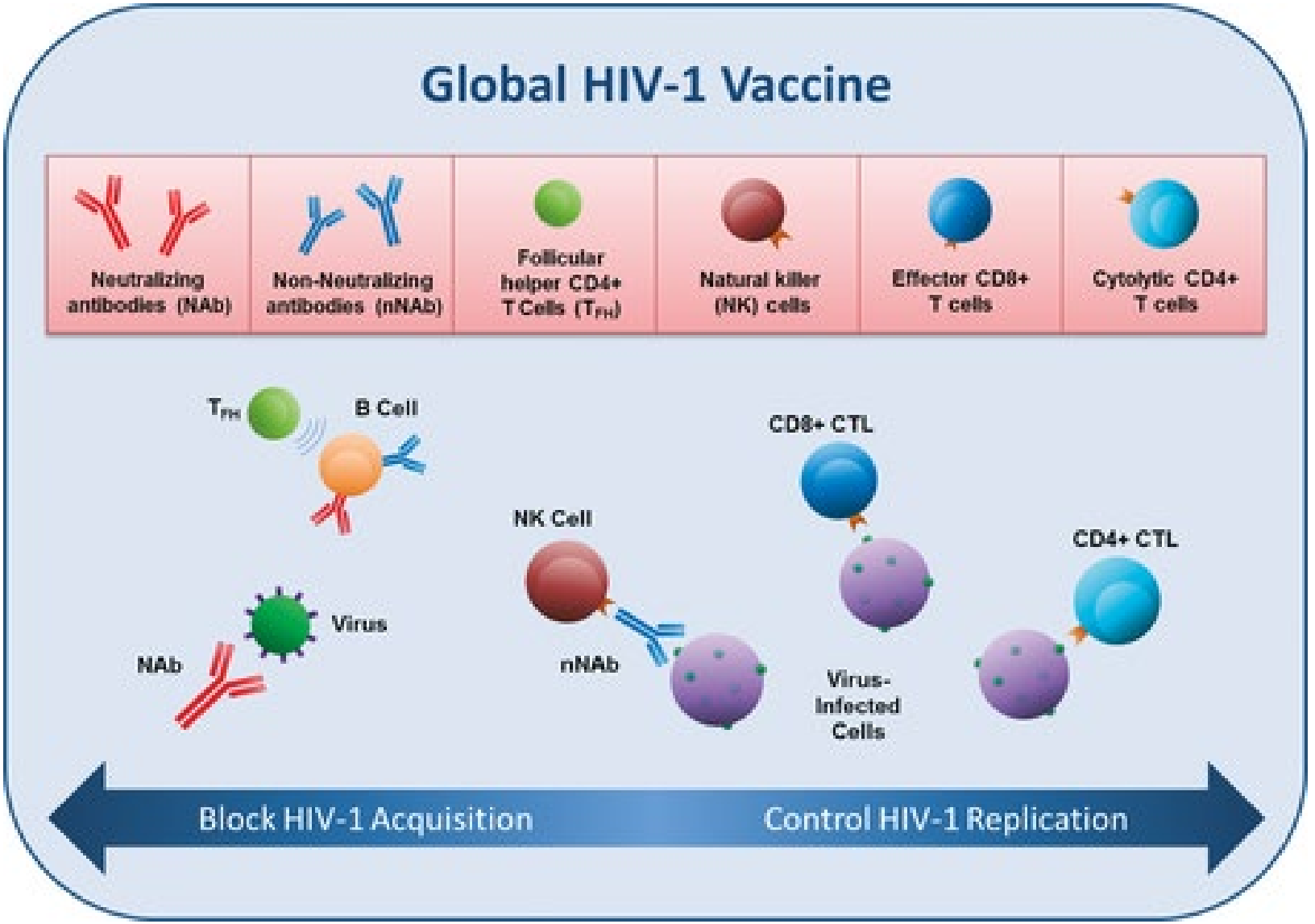
Requirements for vaccine-induced protection and control



Mechanisms of CD8+ T cell-mediated suppression of HIV replication



A global approach to HIV-1 vaccine development



Immunological Reviews
Volume 254, Issue 1, pages 295-304, 16 JUN 2013 DOI: 10.1111/imr.12073
http://onlinelibrary.wiley.com/doi/10.1111/imr.12073/full#imr12073-fig-0001

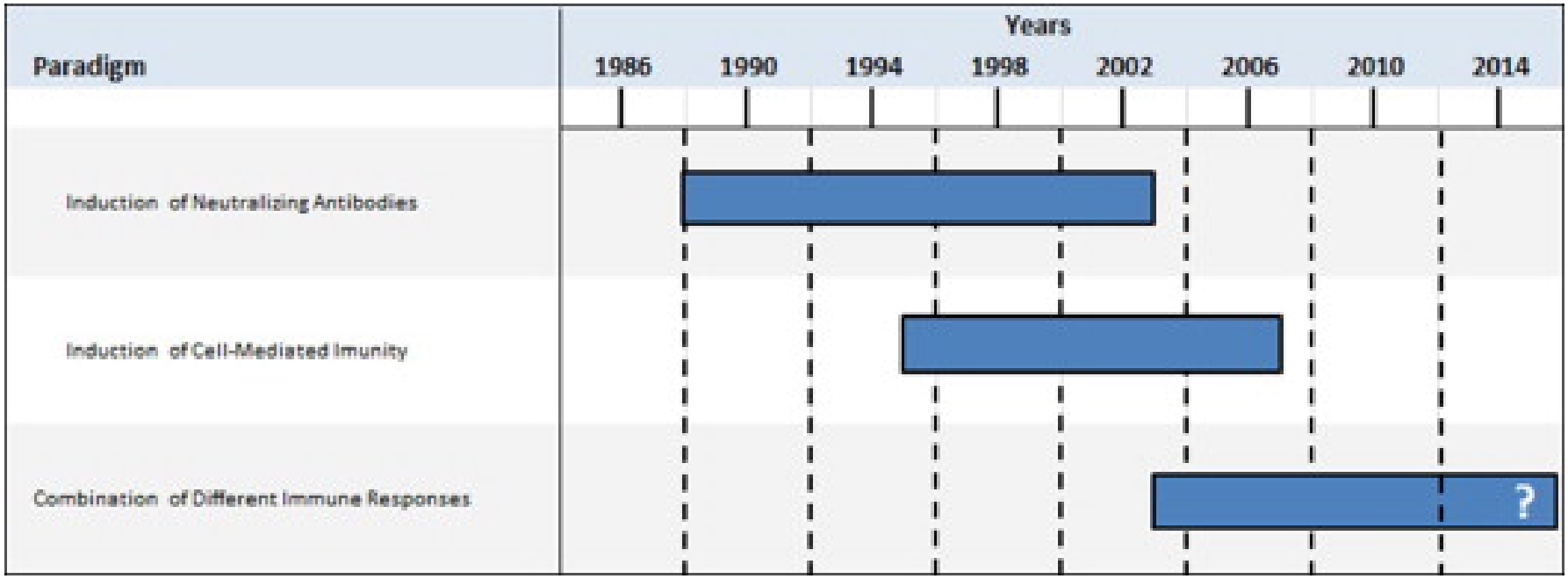


Fig. 1 Evolution of HIV vaccine paradigms and clinical trials.

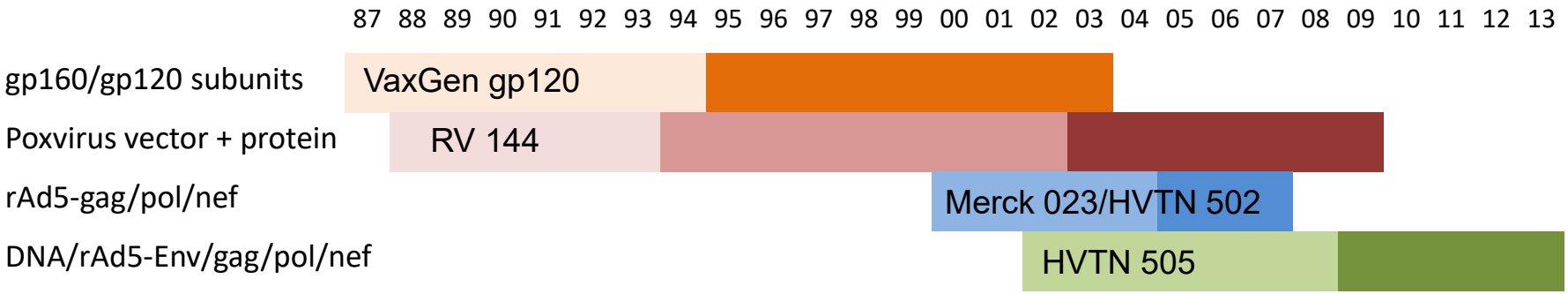
José Esparza

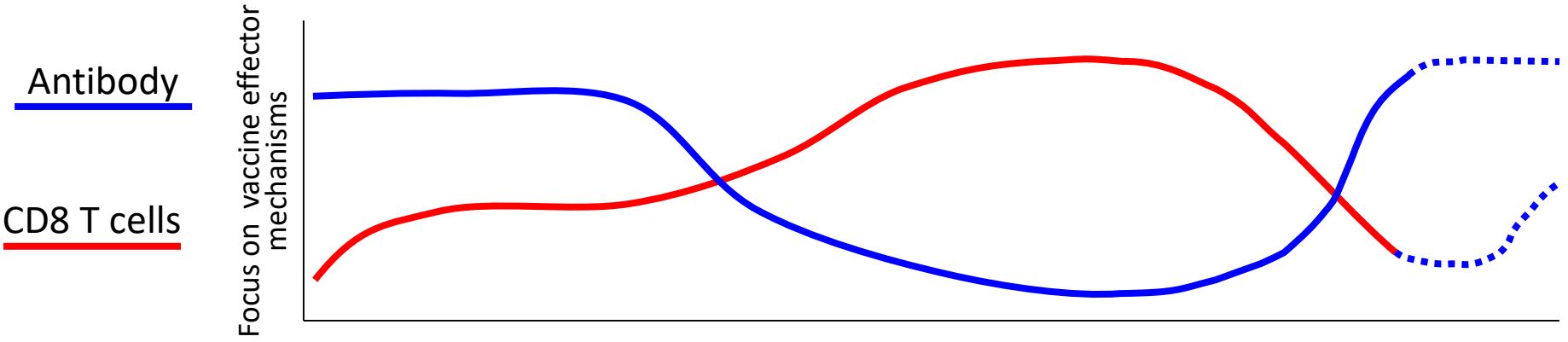
A brief history of the global effort to develop a preventive HIV vaccine

Vaccine Volume 31, Issue 35 2013 3502 - 3518
http://dx.doi.org/10.1016/j.vaccine.2013.05.018

WHAT HAVE WE DONE?

Brief History of HIV Vaccine Efficacy Trials

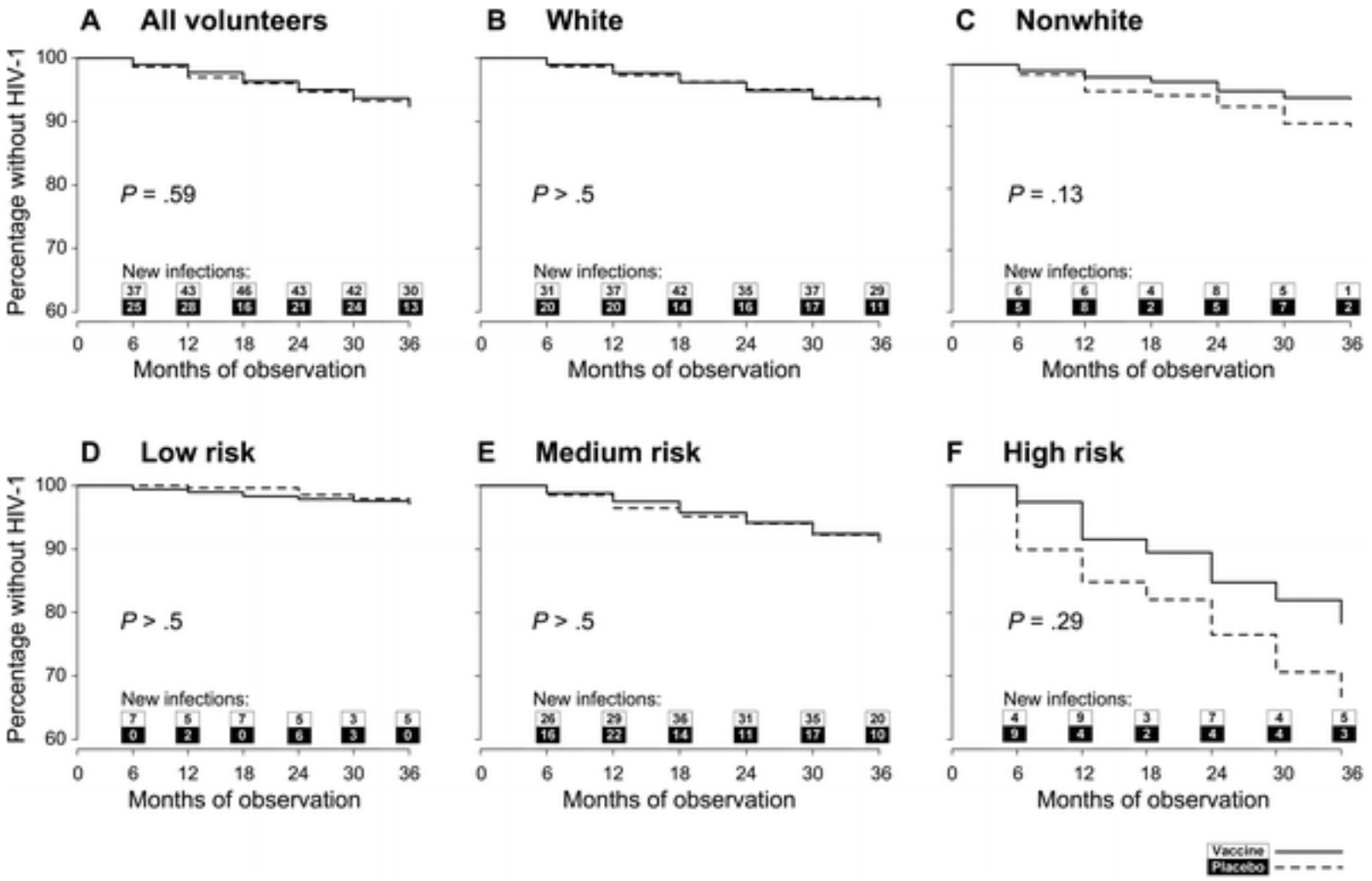




The Journal of Infectious Diseases 2005;191:654–665

Placebo-Controlled Phase 3 Trial of a Recombinant Glycoprotein 120 Vaccine to Prevent HIV-1 Infection

The rgp120 HIV Vaccine Study Group[a]



HIV clinical trials, rationale design and outcome

Study	Regimen	Participants	Aim	Outcome	References
VAX004 (United States, Netherlands)	*r*gp120 B/B	MSM, high-risk women	bnAbs	No prevention of HIV infection	[61,62]
VAX003 (Thailand)	*r*gp120 B/E	Drug users	bnAbs	No prevention of HIV infection	[63,64]
Step/HVTN502 (USA)	*r*Ad5 HIV-1 gag/pol/nef B	MSM, high-risk women	CD8+ T-cells	Increased infection risk	[67]
Phambili/HVTN503 (South Africa)	*r*Ad5 HIV-1 gag/pol/nef B	Heterosexual men, women	CD8+ T-cells	Increased infection risk	[68]
HVTN505	* DNA/*r*Ad5	MSM, transgender women	Ab and T-cells	No infection risk, no efficacy	[69]
RV144 (Thailand)	* ALVAC-HIV/AIDSVAX B/E gp120 in alum	High risk men and women	Ab and T-cells	31.2% vaccine efficacy	[7]

r: recombinant; MSM: men who have sex with men; bnAbs: broadly neutralizing antibodies; *: prime-boost regimen.

Int. J. Mol. Sci. **2018**, *19*, 1241; doi:10.3390/ijms19041241

Step Study (HVTN 502)

IFNγ-secreting HIV-specific T cells in 77% of vaccinees; HIV-specific CD4+ T cells in 41% of vaccinees

The vaccine was highly immunogenic for inducing HIV-specific CD8+ T cells

The HTVN 502 (HIV gag/pol/nef) vaccine did not reduce plasma viremia after infection; HIV-1 incidence was higher in the vaccine-treated group.

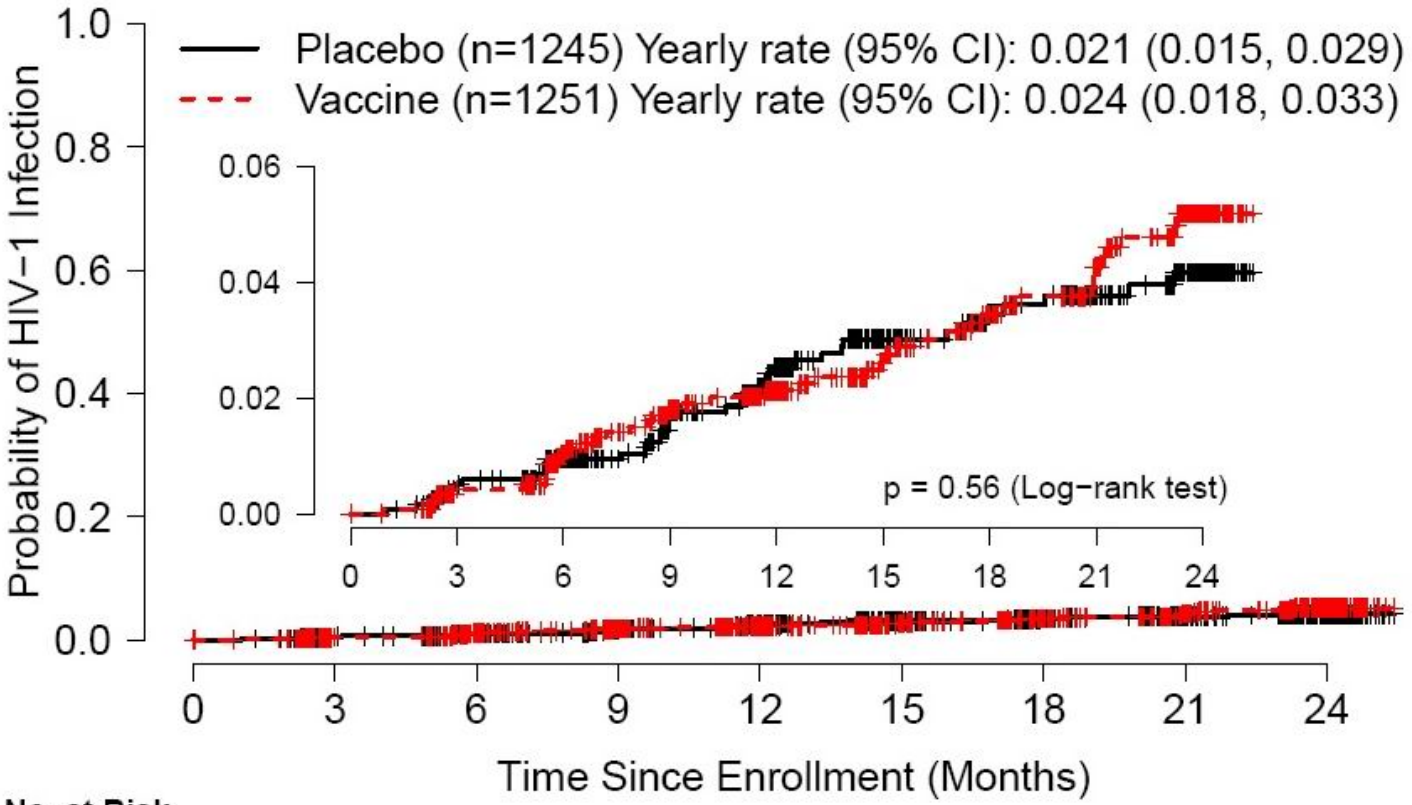
HVTN 505 (DNA/rAd5)

Designed to elicit HIV-specific, multifunctional responses in CD4+ and CD8+ T cells and antibodies to envelopes of the major circulating strains

Efficacy Trial of the HVTN 505 Preventive Vaccine

NEJM October 2013

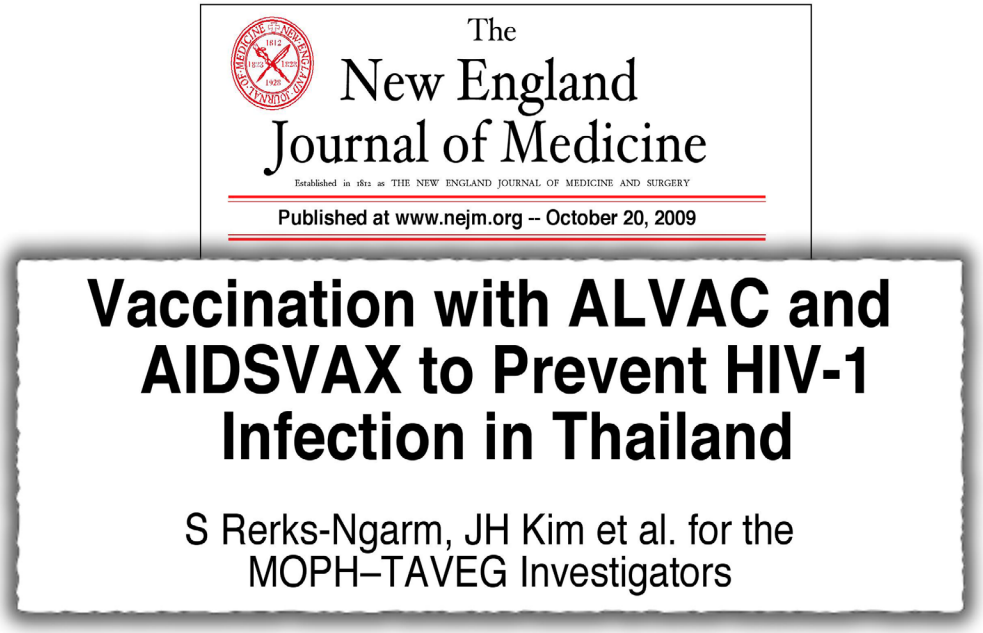
The HVTN 505 clinical trial was interrupted because an an interim review showed that that the vaccine did not prevent HIV infection nor reduce viral load among vaccine recipients who became infected with HIV



No. at Risk									
Placebo	1245	1152	1080	945	837	713	630	543	320
Vaccine	1251	1160	1088	961	856	737	643	563	342
Cumulative No. of Infections									
Placebo	0	6	11	18	26	30	33	35	37
Vaccine	0	5	12	20	23	27	33	38	43

Figure S19: Cumulative incidence of MITT HIV-1 infection based on updated data through August 23, 2013.

RV144: First Signal of HIV Vaccine Efficacy



The New England Journal of Medicine

Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

Published at www.nejm.org -- October 20, 2009

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

S Rerks-Ngarm, JH Kim et al. for the MOPH–TAVEG Investigators

ALVAC®-HIV (vCP1521)

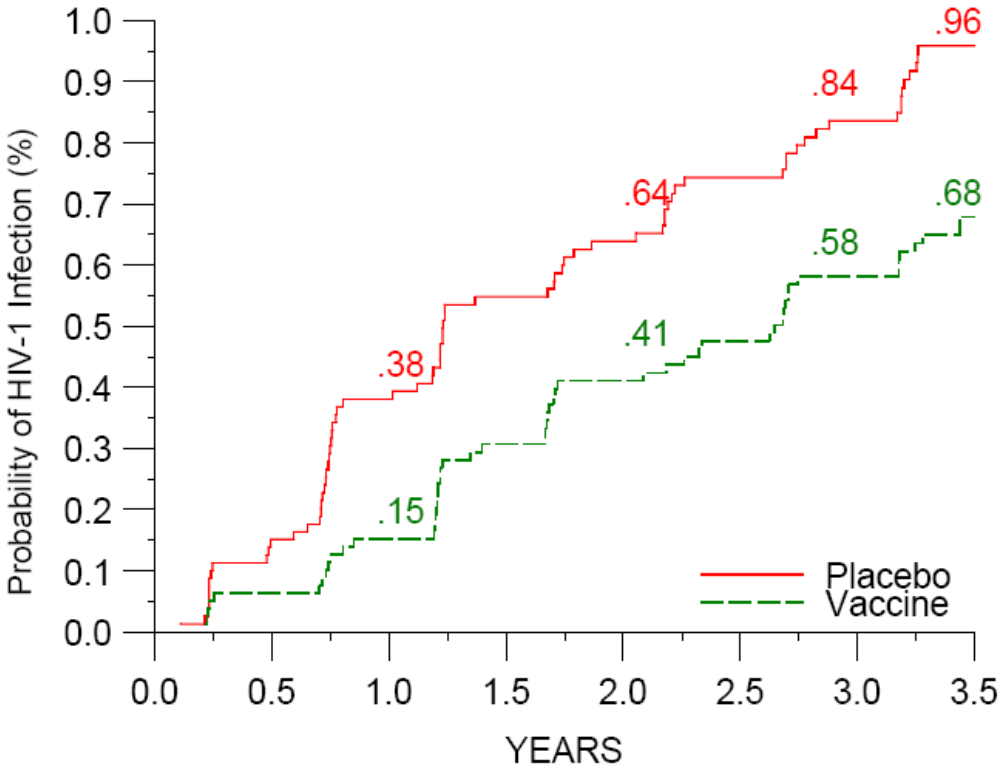
Canarypox expressing HIV-1 subtype E gp120 and HIV-1 subtype B gag and protease

AIDSVAX® B/E

HIV gp120 subtype E and B

Effect on Acquisition (MITT Analysis)

Cumulative # Infections	Placebo	30	50	65	74
	Vaccine	12	32	45	51



# at Risk	P 8198	7775	7643	7441	7325
	V 8197	7797	7665	7471	7347

16,395 subjects
52,985 person-years

125 infections

Vaccine infections: 51
Placebo infections: 74

VE: 31.2%
p=0.04
95% CI: 1.1, 52.1
(O'Brien-Fleming-adjusted)

31% reduction in infection incidence in vaccine arm of study

HIV-1 vaccine efficacy trials: immune correlates of risk

Vaccine regimen	Location/risk population	Overall vaccine efficacy	Increased risk of infection	Immune correlates of decreased vaccine efficacy[a]	Immune correlates of decreased HIV risk	Immune correlates of immune control post infection	Virus sieve	Host genetic correlates
VAX003 (Phase III) Protein/ Alum (CRF01_AE/Clade B Env)[52]	Thailand/injection drug users	No efficacy	No	No	No[52]	No	No[118,b]	n/d
VAX004 (Phase III) Protein/ Alum (Clade B Envs)[53]	USA/MSM/high risk women	No efficacy	No	No	Yes ADCVI, CD4 Blocking, Tier 1 NAb	n/d	No[160,161]	Yes Fcγ receptor IIIa genotype (VV genotype)[125]
STEP HVTN502 (Phase IIb) Ad5 Vector (Clade B Gag/Pol Nef)[54]	North/South America, Australia, Caribbean/MSM and High Risk Hetero-sexual Men and Women	No efficacy[c]	Yes	n/d	No	Yes T cell breadth/ magnitude, Lower VL	Yes[67]	Yes HLA alleles (B*27, B*57, B*58:01), Lower viral load
Phambili HVTN503 (Phase IIb) Ad5 Vector (Clade B Gag/Pol Nef)[57]	South Africa/Hetero-sexual Men and Women	No efficacy[d]	n/d	n/d	n/d	n/d	n/d	n/d
RV144 (Phase III) ALVAC vector (Clade B Gag/Pro + CRF01_ A/E Env) + Protein/ Alum (CRF01_AE/B Env)[50]	Thailand/Community	31% efficacy	No	Yes Plasma Env IgA[71,74]	Yes V1V2 IgG, Linear V2, V1V2 IgG3, Interactions (ADCC, Avidity, Tier 1 NAb, IgA), $CD4^+$ T cell Polyfunction, Cytokines[71–73,75,111]	n/d	Yes[85,162]	Yes HLA A*02 allele[126]: FcγRIIC -118 L allele[114]: DQB1*06[113]
HVTN505 (Phase IIb) DNA/ Ad5 (Clade A, B, C *Env*, *Clade BGag/Pol*)[60]	USA/MSM and TG, Ad5 seronegative, Circumcised	No efficacy[c]	No	No	Yes $CD8^+$ Env T-cell Polyfunction[e]	n/d	Yes[66]	n/d

The six HIV-1 vaccine efficacy studies are listed alongside their corresponding outcomes for vaccine efficacy, immune correlates of risk, and associations of vaccine efficacy with virus sieve analysis and host genetics. Findings with positive outcomes for vaccine efficacy are shaded in blue and findings with negative outcomes for vaccine efficacy are shaded in gray. MSM = Men who have sex with Men; TG = transgender; ADCVI = antibody-dependent, cell-mediated virus inhibition; Tier 1 NAb = neutralizing antibodies that target easy to neutralize viruses (ie not circulating transmitted/founder viruses); V = Valine, FcγRIIIa is encoded by alleles that confer either a phenylalanine (F) or valine (V) at amino acid position 158.

[a]No increased risk of infection compared to the placebo group.

[b]No significant virus sieve that correlated with acquisition. An atypical genetic sieve in the V2 region was identified but also did not correlate with acquisition.

[c]Efficacy futility determined at first interim analysis after full enrollment.

[d]Vaccinations discontinued: unblinded early based on STEP result.

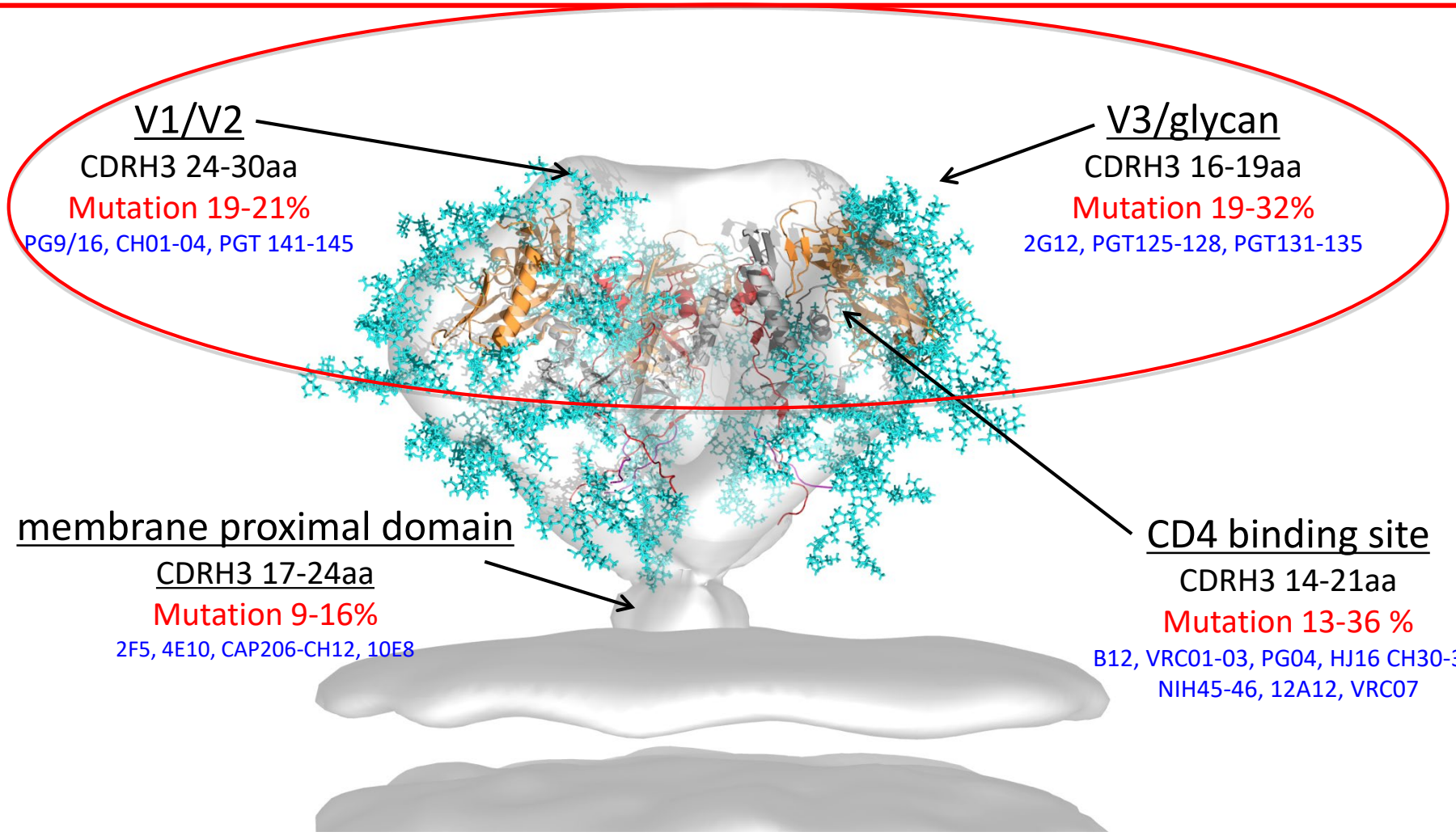
[e]Frahm N, McElrath MJ et al. (2016) Research for Prevention Meeting, Chicago, IL.

10.1371/journal.pone.0075665

Plasma IgG to Linear Epitopes in the V2 and V3 Regions of HIV-1 gp120 Correlate with a Reduced Risk of Infection in the RV144 Vaccine Efficacy Trial

IgG antibodies that bind to V1/V2 recombinant protein correlated inversely with infection rate

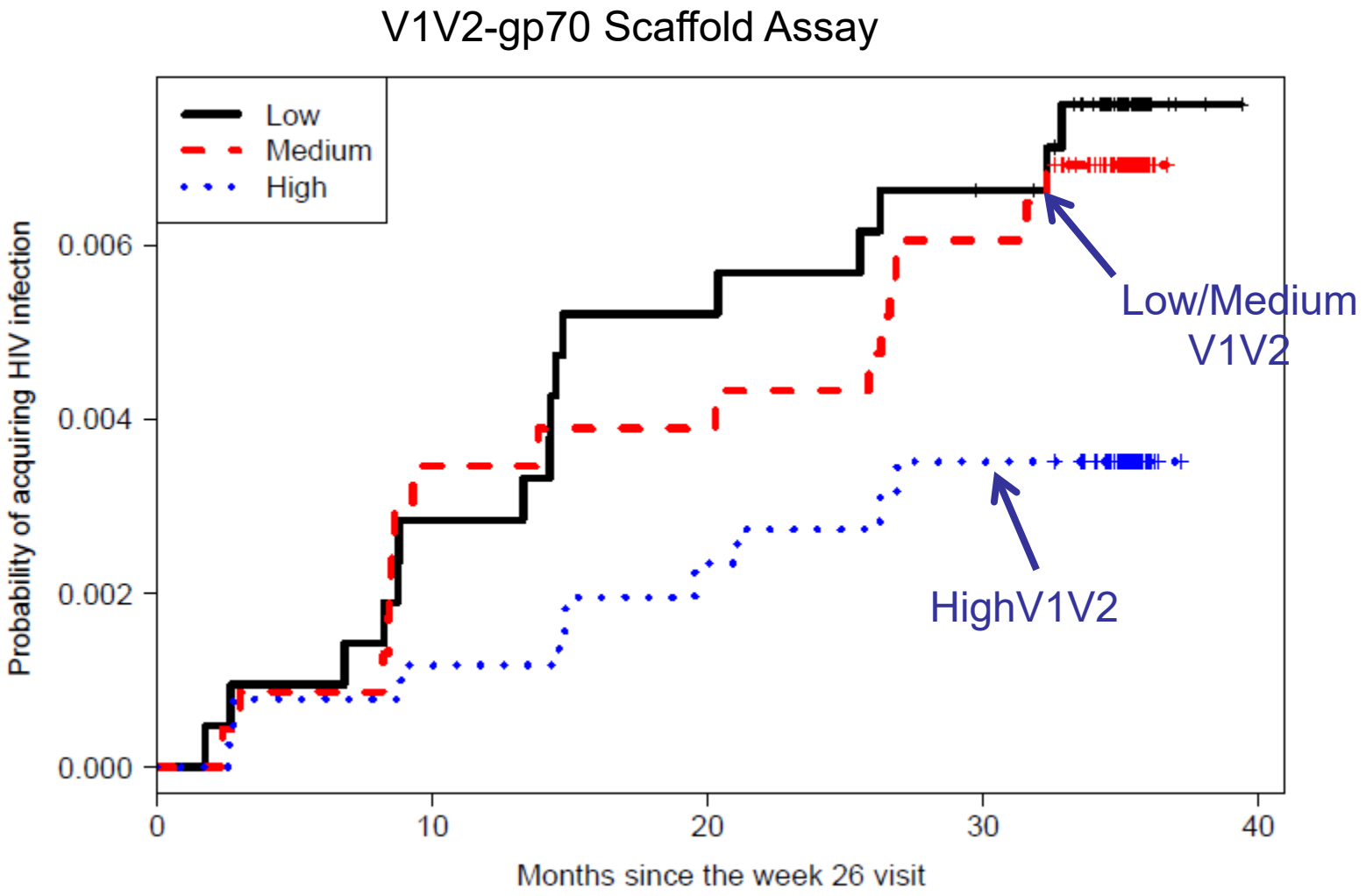
Sites of Vulnerability for HIV Neutralization



Haynes *et al.* (2012) *Nat.Biot.* 5: 423-433
Kwong and Mascola *et al.* (2013) *Immunity.* In Press

Long CDRH3 loops and minimal Somatic Hypermutation (SHM)

Cumulative Infection Rates



Thai Vaccine ('RV144') what's next?

Several small-scale clinical trials in southern Africa, started January 2015 and ongoing

A large-scale trial (HVTN 702) launched in October 2016, using a similar regimen to RV144, but made for South Africa; the trial is ongoing

SO, DO WE HAVE A VACCINE?

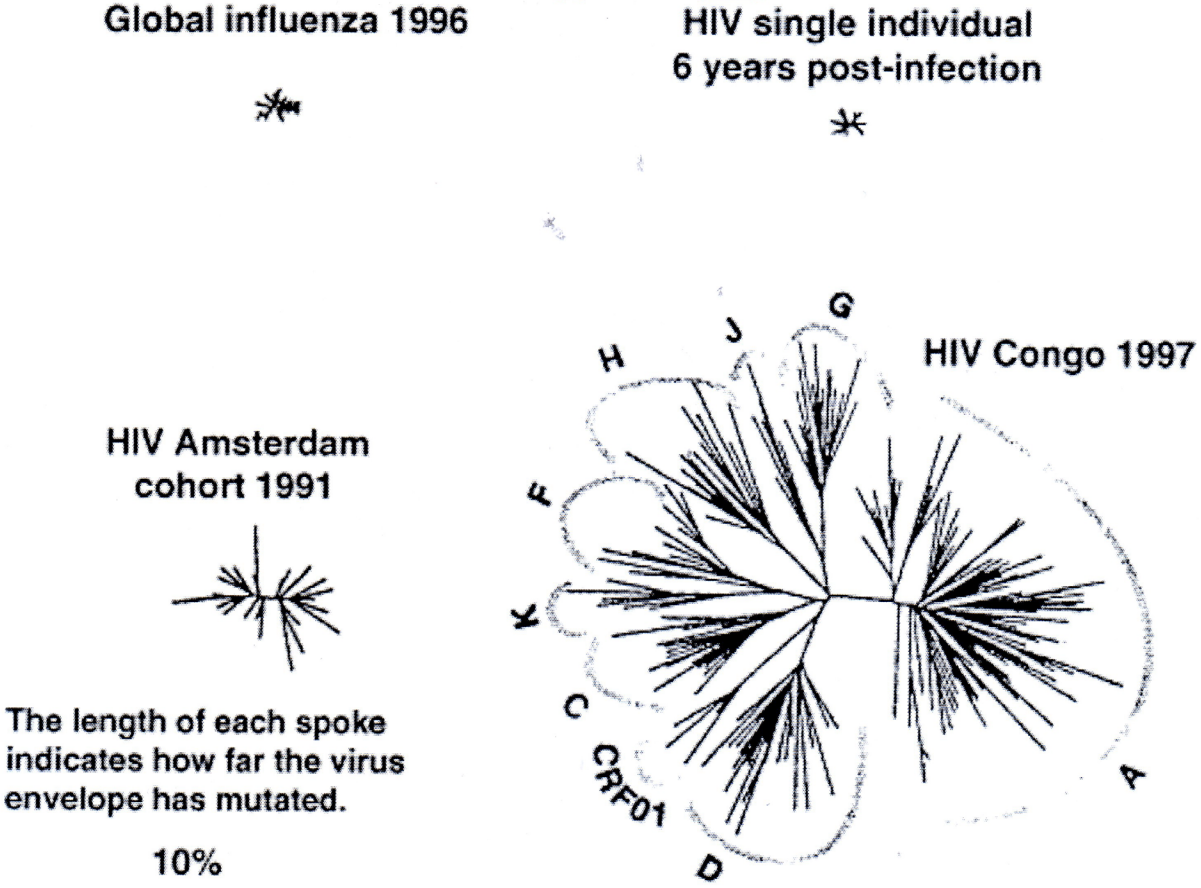
NO

- How do you induce V1-V2 Ab?
- Why are they induced only in some vaccinees?
- How do the V1-V2 Ab work?
- Are they enough?

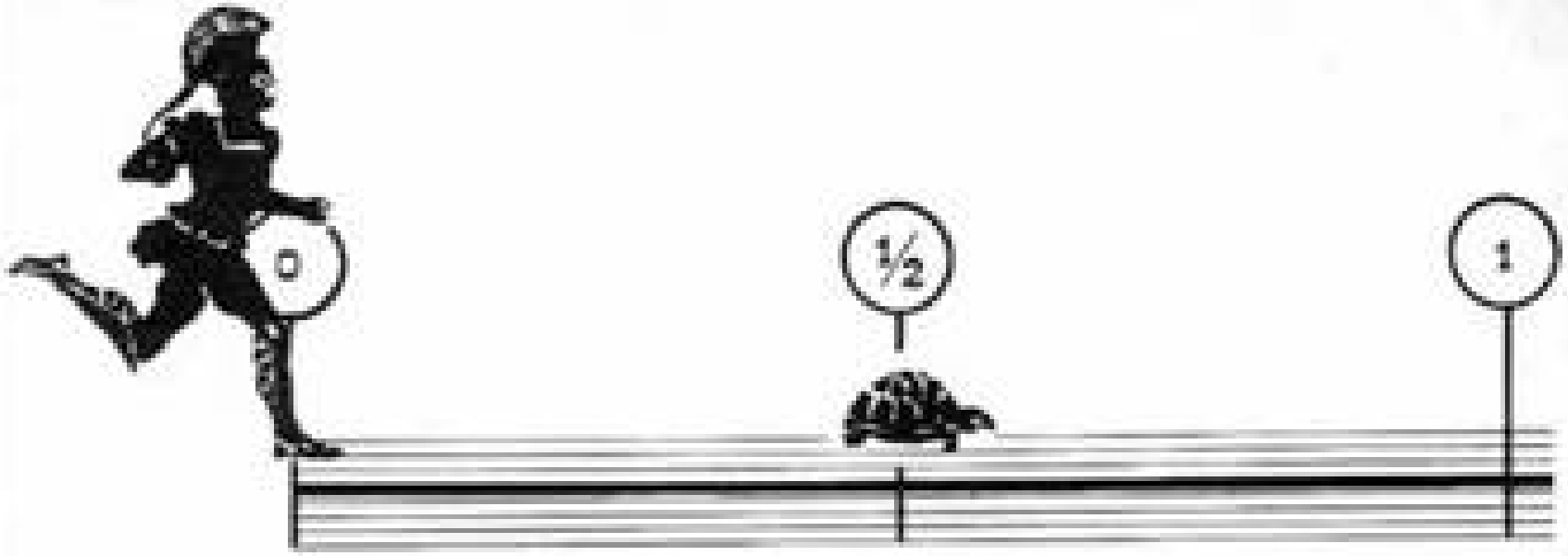
WHY DONT WE HAVE A VACCINE?

Hypervariablity of HIV

Fig. 2. Genetic diversity of human immunodeficiency virus envelope glycoprotein gp120 compared with that of H3N2 influenza virus haemagglutinin [36].



alla partenza



quando Achille ha percorso l'handicap

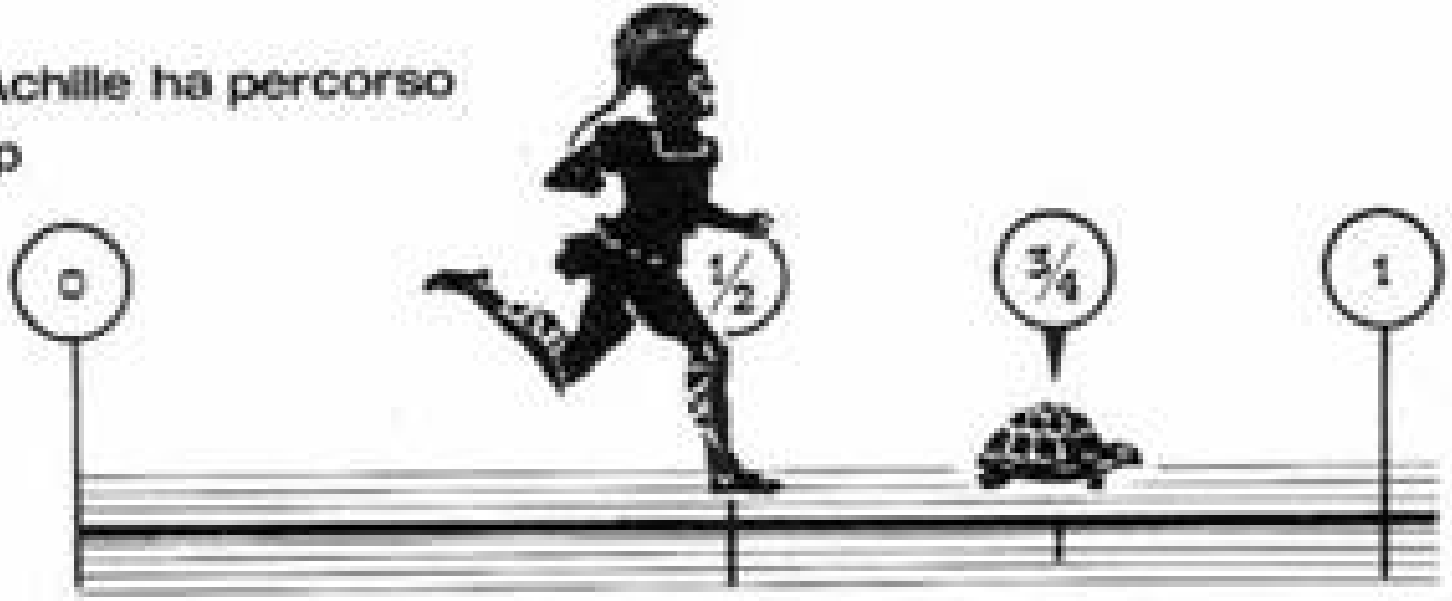
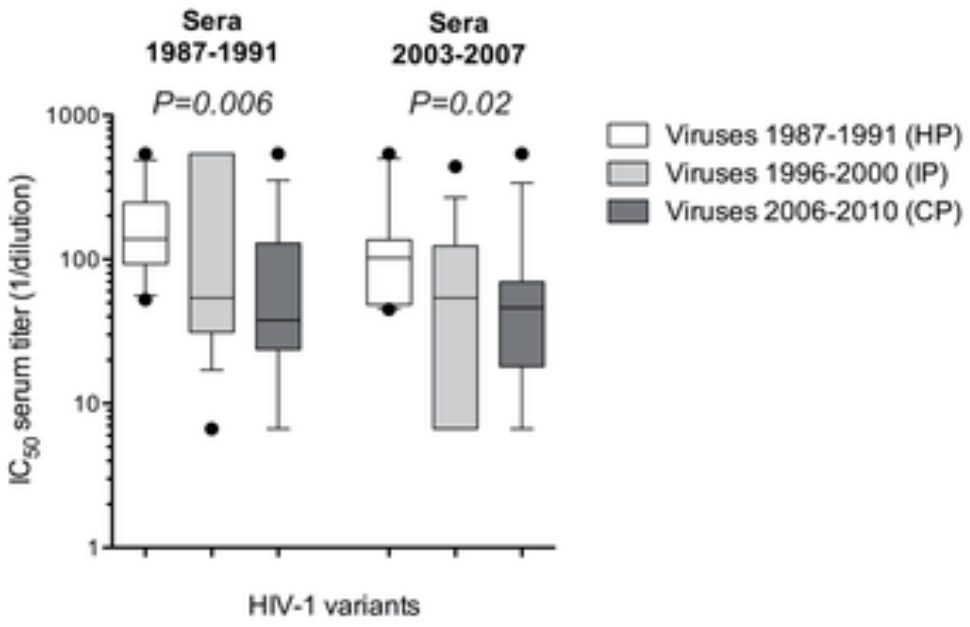


Figure 1. Enhanced resistance of clade B early/transmitted HIV-1 variants to neutralization by polyclonal sera over the course of the epidemic.

A



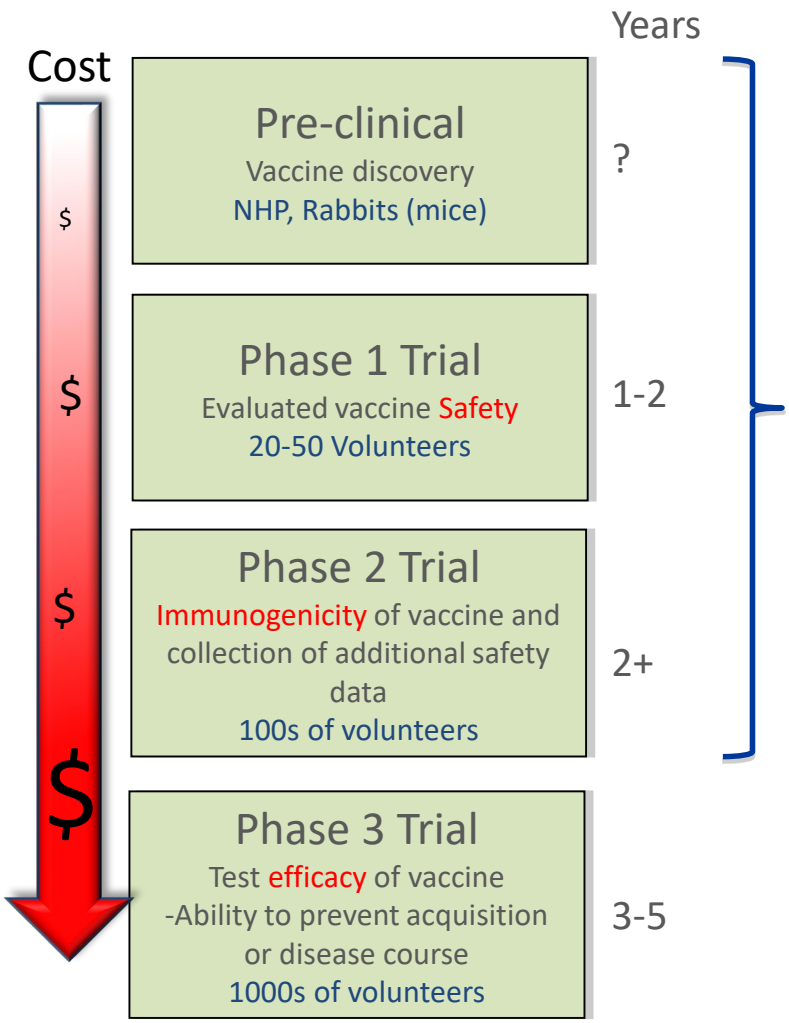
B

	% of viruses neutralized IC50 ≥ 20			Chi² test for trend	% of viruses neutralized IC50 ≥ 100			Chi² test for trend
Sera	1987-1991 (HP)	1996-2000 (IP)	2006-2010 (CP)		1987-1991 (HP)	1996-2000 (IP)	2006-2010 (CP)	
1987-1991	100.0	93.3	92.9	*NS*	63.6	40.0	35.7	*NS*
2003-2007	100.0	73.3	85.7	*NS*	54.6	33.3	14.3	*P=0.03*

Key : > 90% | 60-90% | 30-60% | 1-30%

Bouvin-Pley M, Morgand M, Moreau A, Jestin P, et al. (2013) Evidence for a Continuous Drift of the HIV-1 Species towards Higher Resistance to Neutralizing Antibodies over the Course of the Epidemic. PLoS Pathog 9(7): e1003477. doi:10.1371/journal.ppat.1003477
http://www.plospathogens.org/article/info:doi/10.1371/journal.ppat.1003477

Development Pathway for HIV Vaccines



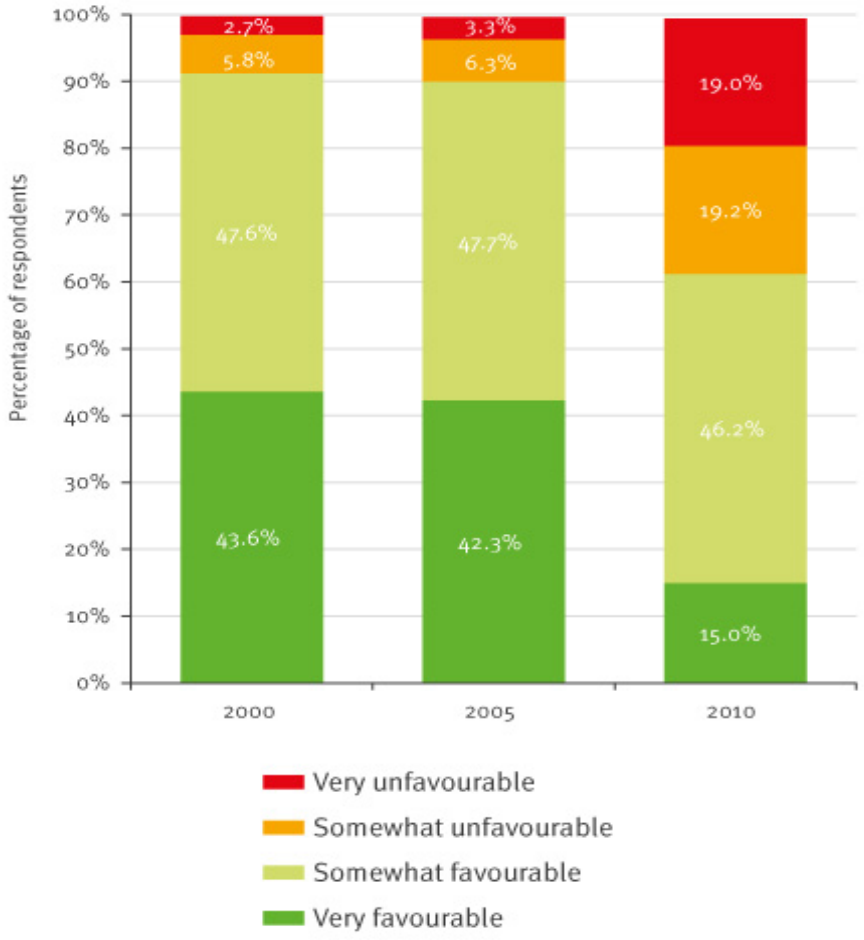
Thai trial≈ $120 million

Immunogenicity: measurements made to gauge the size of an effective immune response

Problem: we don't really know what an effective immune response is for HIV infection

FIGURE 1

Attitudes towards vaccination in general in the population aged 18–75 years, INPES surveys, France, 2000, 2005, 2010



INPES: French National Institute for Prevention and Health